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Tetrahedron: *Asymmetry* 15 (2004) 617–625
Tetrahedron: *Asymmetry*

Chemoenzymatic synthesis of enantioenriched 5-oxo-tetrahydro-3-furancarboxylic acid derivatives

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Received 3 October 2003; revised 23 December 2003; accepted 5 January 2004

Abstract—(*R*)-(+)-Paraconic acid **4**, (*S*)-(−)-terebic acid **6** and their corresponding methyl and ethyl esters having ee's ranging from 60% to 92% were obtained by enzymatic resolution of their racemates. The enzymatic resolution of racemic ethyl γ-methylparaconates **14a** and **14b** allowed the isolation of the unreacted ester (2*R*,3*R*)-(+)-**14a** and that of the lactonic acid (2*S*,3*R*)-(−)-**5b** with 80% and 93% ee, respectively, the former by the use of Horse liver acetone powder (HLAP), the latter using α-chymotrypsin (α-CT). The enantiomeric ethyl (2*S*,3*S*)-(−)-**14a** and (2*S*,3*R*)-(−)-**14b**, both with >99% ee, were obtained by baker's yeast reduction of diethyl acetylsuccinate.

1. Introduction

5-Oxo-tetrahydro-3-furancarboxylic acid derivatives, commonly known as paraconic acid derivatives constitute a small class of highly substituted γ-butyrolactones, which are metabolites of mosses, lichens and fungi.[1] They are characterised by the presence of the carboxylic group at the β-carbon atom of the lactone ring. As natural compounds, paraconic acid derivatives are also functionalised at the γ-carbon atom with an alkyl chain and at the α-position with either a methyl[1b,2] or a methylene[1c,1d] group. Examples are rocellaric acid (−)-**1**,[3] phaseolinic acid (−)-**2**[4] and methylenolactocin (−)-**3**[5] (Fig. 1). The bioactivity observed for this latter compound, in particular as an antitumoural and antimicrobial agent,[6] has been ascribed to the presence of the α-methylene group, which could undergo nucleophilic attack by biological nucleophiles.[7]

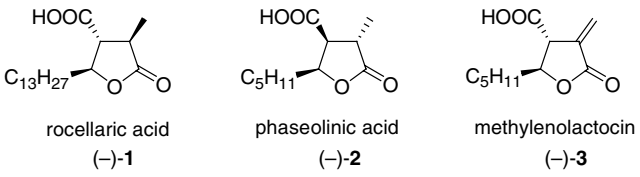

Figure 1.

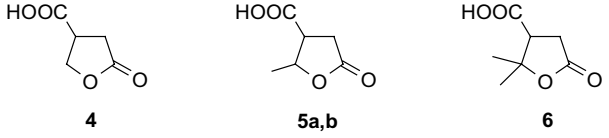

Figure 2.

The first member of the series, paraconic acid **4**,[8] namely 5-oxo-tetrahydro-3-furancarboxylic acid (Fig. 2), is non-natural but it is an important intermediate in the synthesis of *A*-factor,[9] an inducer of the biosynthesis of streptomycin in inactive mutants of *Streptomyces griseus*, firstly isolated by Khokhlov et al.[10] in 1973. The esters of paraconic acid have industrial applications, especially in the perfume industry and solvent production.[11] In 1965, Tocanne and Asselineau[8] assigned the absolute *R* configuration to (−)-paraconic acid, which was later corrected to *S*.[12] In 1983, Mori[13] demonstrated that the absolute configuration of (−)-**4** was *S*, bringing an end to the controversy concerning the stereochemistry of paraconic acid.[14]

The present work deals with the chemoenzymatic syntheses of enantiomerically enriched paraconic acid **4**, its γ-methyl diastereomeric derivatives **5a**,**b** and its γ,γ-dimethyl derivative **6** (Fig. 2) as well as their respective esters **11**–**14** (Scheme 1). The scope was to ascertain the influence of one or two methyl groups at the γ-position

Keywords: Lactones; Enzymatic resolution; Baker's yeast; Circular dichroism; Paraconic acids.
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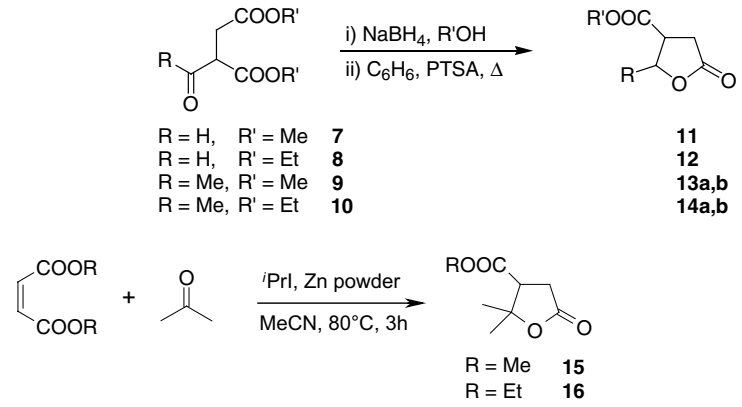
doi:10.1016/j.tetasy.2004.01.001



Scheme 1.

on the efficiency of the enzymes used in the enantiodifferentiating step. The presence of a gem-dimethyl group was also of interest, owing to the attention recently paid to terebic acid **6** as a possible antitumoural agent.[15]

2. Results and discussion

2.1. Synthesis of the substrates

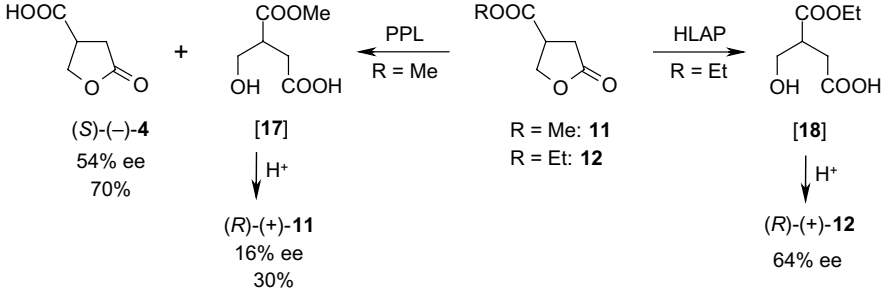
Methyl and ethyl paraconates, **11** and **12**, respectively, were synthesised by reduction of the corresponding dimethyl and diethyl formylsuccinates, **7** and **8**, respectively, with $NaBH_4$ in alcohol,[16] followed by lactonisation of the resulting dialkyl hydroxymethylsuccinate intermediates under acidic conditions (Scheme 1).

Starting from dimethyl and diethyl acetylsuccinates, **9** and **10**, respectively, also methyl and ethyl γ-methylparaconates, **13** and **14**, were prepared by the same procedure. Both compounds **13** and **14** were obtained as mixtures of *cis* and *trans* diastereomers **a** and **b**, initially in the ratio of 3:1 and 3:2, respectively, in favour of the *cis* diastereomers. An equilibration of both mixtures, carried out in refluxing toluene with DBU added, afforded the thermodynamically controlled mixtures whose compositions were 9:1 in favour of the *trans* isomers. From the kinetically controlled mixtures, the *cis* isomers **13a** and **14a** were obtained as pure compounds by flash chromatography, while the isomerically pure *trans* isomers **13b** and **14b** were obtained in the same manner from the respective thermodynamically controlled mixtures.

Methyl and ethyl terebate, **15** and **16**, respectively, were synthesised from dialkyl maleate, isopropyl iodide and acetone under the catalysis of zinc powder, in accordance with a literature procedure (Scheme 1).[17]

2.2. Enzymatic hydrolyses of 11 and 12

The enzymatic hydrolyses of racemic methyl and ethyl paraconates **11** and **12**, carried out at 20% conversion with HLAP and PPL proved different, at least as far as the chemoselectivity is concerned. In fact, while the methyl ester **11** underwent hydrolysis at both the methoxycarbonyl group and the lactone function, furnishing (*S*)-(−)-paraconic acid **4** (54% ee from PPL) $\{[\alpha]_D^{25} = -22.4$ (*c* 0.62, MeOH) [lit.[9] $[\alpha]_D^{25} = -60.0$ (*c* 2.08, MeOH)]} and the hemi-ester (*R*)-**17** (16% ee), the ethyl ester **12** reacted essentially at the lactone group, resulting in the formation of the hemi-ester (*R*)-**18** (64% ee from HLAP). It must be noted that in all cases in which opening of the lactone ring occurred, the resulting hemiesters were analysed as their ring closure products, (*R*)-(+)-**11** and (*R*)-(+)-**12** in the present case. The above mentioned enzymes were chosen in as much as they catalysed a very rapid hydrolysis. In fact the time required to hydrolyse **11** and **12** was 53 and 4 min, respectively. Chemical hydrolysis under the same conditions proceeded on the ester groups of **11** in 6 h and mainly on the lactone group of **12** in 16 h, for an amount



Scheme 2.

of 20% in both cases. The best results for the low reaction conversions are summarised in Scheme 2.

An improvement in the enantiomeric excesses of the lactonic esters **11** and **12** was achieved carrying out the hydrolyses with PPL to 80% conversion. The unreacted methyl paraconate (*R*)-(+)-**11** was isolated with 92% ee while the unreacted ethyl ester (*R*)-(+)-**12** was obtained with 93% ee. Their chemical hydrolyses under acidic conditions furnished paraconic acid (*R*)-(+)-**4** with 80% ee, owing to a partial racemisation. Other enzymes were also checked, such as *Candida cylindracea* lipase (CCL), lipase from *Pseudomonas* sp. (PS), *Mucor miehei* lipase (MML), *Candida antarctica* lipase (CAL), α-chymotrypsin (α-CT) and subtilisin, a protease from *Bacillus subtilis*, which all showed very low enantioselectivity. Porcine liver acetone powder (PLAP) and lipase from *Aspergillus niger* (AP12) were not enantioselective at all.

2.3. Enzymatic hydrolyses of 13a, 14a and 13b, 14b

A check, carried out in phosphate buffer at pH 7.4 at room temperature for 30 h aimed at verifying a possible chemical hydrolysis, revealed that, for the *cis* isomers **13a** and **14a**, opening of the lactone ring occurred preferentially to an amount not exceeding 15%, while the *trans*-methyl ester **13b** underwent hydrolysis to an amount of 20% and the *trans*-ethyl ester **14b** remained unchanged.

The best results found for enzymatic hydrolyses carried out on the *cis* diastereomers **13a** and **14a** to 20% conversion are given in Scheme 3. Chemo- and enantioselective hydrolysis of the lactone group of **14a** was observed for HLAP, from which (2*R*,3*R*)-(+)-**14a** with 80% ee was isolated, after cyclisation of the intermediate **20a**. On the contrary, the hydrolysis of **13a** with CAL was moderately enantioselective and not chemoselective. In fact the corresponding acid (2*S*,3*S*)-(−)-**5a** having 38% ee was obtained, together with racemic **13a**, after cyclisation of the intermediate **19a**.

The crude enzyme PLAP proved somewhat inefficient on both substrates showing however poor chemoselectivity and moderate enantioselectivity. α-CT and subtilisin were effective on both substrates **13a** and **14a** but with low enantioselectivity, while CCL, lipase AP12, lipase PS and MML showed no enantioselectivity at all. Enzymatic hydrolyses of the *trans* diastereomers **13b** and **14b** were more satisfactory in that no formation of ring fission products was observed (Table 1).

α-Chymotrypsin exhibited the highest *E* values[18] for both substrates, allowing the isolation of the acid (2*S*,3*R*)-(−)-**5b** with 93% ee. Among the hydrolases listed in Table 1, PLAP exhibited the opposite enantiopreference with respect to α-CT, although with a lower *E* value. Other hydrolases such as CCL, CAL, subtilisin, lipase AP12 and lipase PS showed complete lack of enantioselectivity.

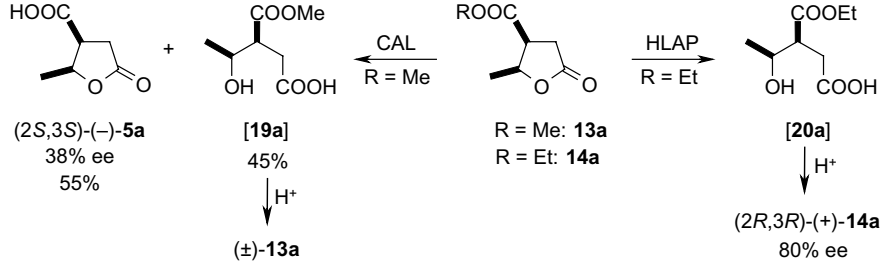
2.4. Enzymatic hydrolysis of 15 and 16

A screening made on the above mentioned hydrolases revealed that only HLAP and PLAP could be used as enantiodifferentiating agents on the methyl and ethyl esters of terebic acid, **15** and **16**, although the *E* values were low in both cases. Both enzymes exhibited the same chemo- and enantiopreference, as they catalysed the hydrolysis of the lactone group only, leading at 20% conversion to the corresponding open chain products **21** and **22**, not isolated, whose acidic treatment led to (*R*)-(+)-**15** and (*R*)-(+)-**16**, the former with 48% ee (from HLAP) and 32% ee (from PLAP) and the latter with 62% ee in both cases (Scheme 4).

A better enantiomeric excess for the methyl ester derivative **15** was obtained using HLAP at high conversion values, after two cycles. Thus (*S*)-(−)-**15** was obtained with 76% ee, from which terebic acid (*S*)-(−)-**6** was obtained with 60% ee, on acidic hydrolysis, owing to partial racemisation.

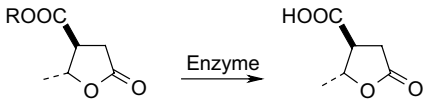
2.5. Bioreductions of the dialkyl acylsuccinates 8, 9 and 10 with baker's yeast

In an alternative approach to the target molecules, the acyl diesters **8**–**10** were reduced with *Saccharomyces cerevisiae* (baker's yeast)[19] using the conditions reported in the literature.[20] Diethyl formylsuccinate **8**,[21] which exists in the enolic form for about 50%, was easily reduced to the corresponding hydroxy derivative **23**, which was isolated and characterised spectroscopically (Scheme 5). Since the chiral columns available did not separate its enantiomers, compound **23** was cyclised to ethyl paraconate **12**, whose HRGC revealed that it was a racemate.



Scheme 3.

Table 1. Enzymatic hydrolyses of **13b** and **14b** at 20% conversion

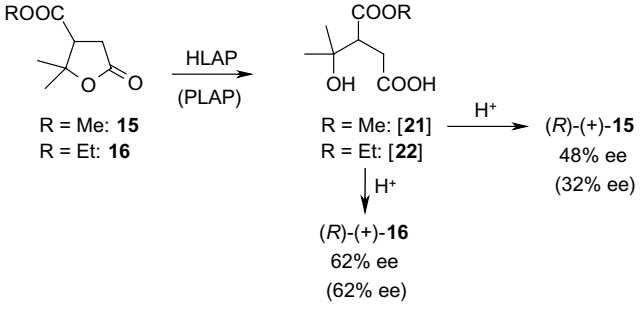


R = Me: **13b**
R = Et: **14b**

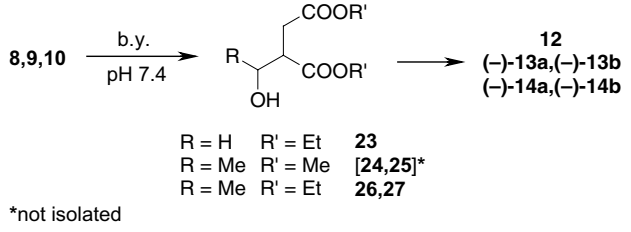
5b

Enzyme	Hydrolysis of (±)-**13b**				Hydrolysis of (±)-**14b**			
	E	Time (min)	Acid **5b**	Unreacted ester **13b**	*E*	Time (min)	Acid **5b**	Unreacted ester **14b**
			Ee (%)[a] Abs. conf.	Ee (%)[a] Abs. conf.			Ee (%)[a] Abs. conf.	Ee (%)[a] Abs. conf.
α-CT	12	35	79 2*S*,3*R*	40 2*R*,3*S*	36	10	93 2*S*,3*R*	28 2*R*,3*S*
PLAP	4	5	56 2*R*,3*S*	19 2*S*,3*R*	3	5	51 2*R*,3*S*	14 2*S*,3*R*
PPL	3	120	42 2*S*,3*R*	15 2*R*,3*S*	2	60	36 2*S*,3*R*	15 2*R*,3*S*

[a] Determined by chiral HRGC on a γ-CDX column.



Scheme 4.



Scheme 5.

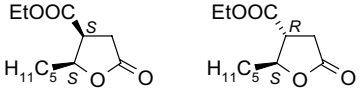
Bioreduction of dimethyl acetylsuccinate **9** resulted in the eventual formation of the corresponding lactones (−)-**13a** and (−)-**13b** having >99% ee's, through the intermediacy of the corresponding hydroxy diesters **24** and **25**, not isolated (Scheme 5). However the chemical yields in isolated products were low. On the contrary, the same biotransformation carried out on diethyl acetylsuccinate **10** resulted in the formation of the corresponding hydroxy diesters **26** and **27** as a 1:1 mixture of *syn* and *anti* diastereomers, which were identified spectroscopically (Scheme 5). Their cyclisation to the corresponding lactones (−)-**14a** and (−)-**14b** was easily accomplished even in deuteriated chloroform at room temperature. These latter compounds were separated and their analyses on chiral HRGC revealed that both ee's were above 99%. Compounds (−)-**14a** and (−)-**14b** were isolated in 24% and 22% overall yield, respectively.

2.6. CD spectra and determination of the absolute configurations of the optically active lactones

The absolute configurations of the lactonic esters bearing two stereocentres were assigned by comparison of their CD spectra with similar molecules of known absolute configuration. Thus the CD curves of the *cis* diastereomers (−)-**13a** and (−)-**14a** were compared with that of ethyl (2*S*,3*S*)-(−)-2-*n*-pentyl-5-oxo-tetrahydrofurancarboxylate **28a**[22] (Fig. 3) and those of the *trans* diastereomers (−)-**13b** and (−)-**14b** were compared with the CD curve of (2*S*,3*R*)-(−)-2-*n*-pentyl-5-oxo-tetrahydrofurancarboxylate **28b**.[23]

The CD spectra for the two series are reported in Figures 4 and 5, which also include the curves for the corresponding *cis* and *trans* acids (−)-**5a** and (−)-**5b**. The CD curves of the *cis* derivatives (Fig. 4), which are all laevorotatory, exhibit a positive Cotton effect in the range 220–230 nm for the n → π* transition. Therefore the (2*S*,3*S*) configuration can be assigned to the stereocentres of (−)-**5a**, (−)-**13a** and (−)-**14a**. Similarly, the *trans* derivatives show a negative Cotton effect in the same range (Fig. 5), demonstrating that the absolute configuration of all compounds (−)-**5b**, (−)-**13b** and (−)-**14b** is (2*S*,3*R*).

As a consequence of the fact that all lactones examined possess the *S* configuration at the γ-carbon atom, it is likely to assume that the sign of the Cotton effect does depend solely on the configuration of the β-carbon atom. The Cotton effect is positive when this stereocentre is *S*, it is negative when this stereocentre is *R*.



(−)-**28a** (−)-**28b**

Figure 3.

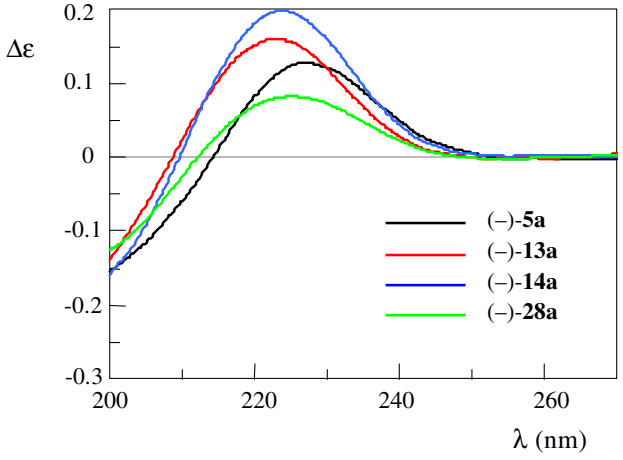


Figure 4.

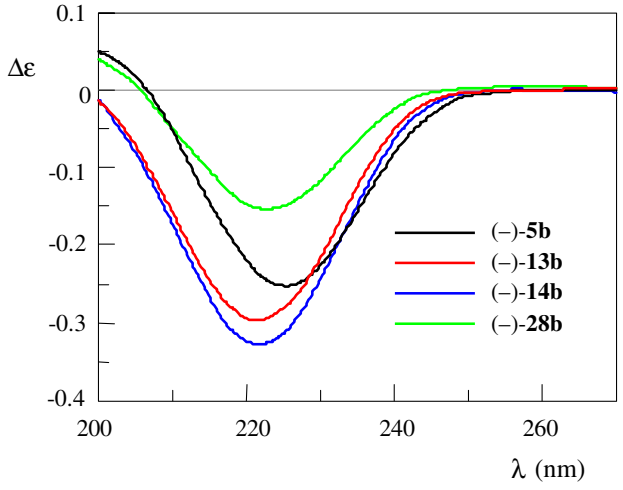


Figure 5.

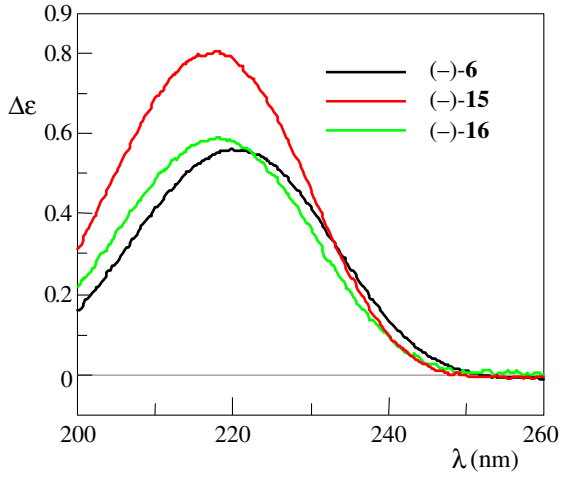


Figure 6.

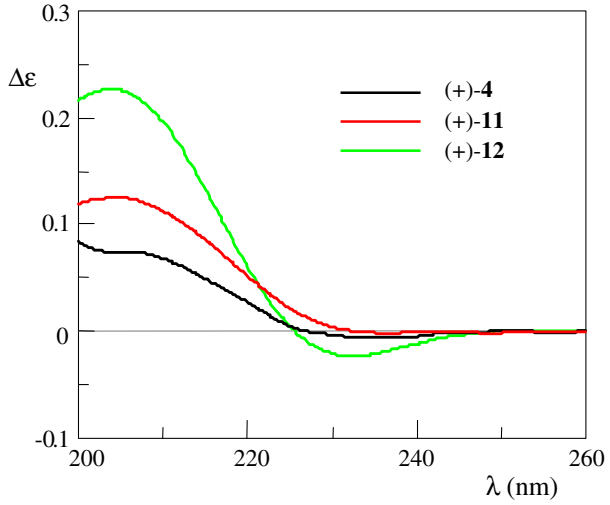


Figure 7.

This statement is also supported by the analysis of the CD curves of terebic acid (−)-**6** and its methyl and ethyl esters (−)-**15** and (−)-**16** (Fig. 6). The absolute configuration of laevorotatory terebic acid **6** is *S*.[24] The CD curves of (−)-**6** and its methyl and ethyl esters (−)-**15** and (−)-**16** are shown in Figure 6, from which it is evident that also their configuration is *S*.

The absolute configuration of methyl paraconate (+)-**11** is *R*,[25] as it is that of ethyl paraconate (+)-**12**. Paraconic acid and esters with *R* absolute configuration show a positive Cotton effect (Fig. 7) for the n → π* transition absorbing between 200 and 210 nm. The curve of (+)-**12** is bisignate, with a weak negative band at around 230 nm, which could be due to the presence of an additional low energy conformation of the lactone ring. As known, in fact, the sign of the Cotton effect depends on both the absolute configuration and the chirality of the lactone ring itself.[26]

3. Conclusions

Paraconic and terebic acid methyl and ethyl esters are not good substrates for enzymatic hydrolyses. In fact all the hydrolases examined exhibited low enantioselectivity. However, it is interesting that terebic acid esters undergo hydrolysis at the lactone group exclusively, probably because of the steric hindrance exerted on the approaching enzyme by the geminal methyl groups, which prevent the carbonyl group of the alkoxycarbonyl group to be coordinated by the active site. In fact, the diastereomeric alkyl *trans*-γ-methylparaconates are hydrolysed regioselectively at the alkoxycarbonyl group and with high enantiopreference. This is a consequence of the preferential attack of the nucleophile of the enzyme active site from the less sterically hindered face of the carbonyl group. On the contrary, the alkyl *cis*-γ-methylparaconates, which are more sterically crowded,

undergo reaction on both carbonyl groups. The behaviour observed for the alkyl γ-methylparaconates parallel that already seen for enzymatic resolution of alkyl γ-*n*-pentylparaconates,[2b,22,23] thus suggesting that it might be due to a higher conformational mobility of the *cis*-disubstituted lactone ring with respect to the *trans* one.

4. Experimental

4.1. General

IR spectra were recorded on a Jasco FT/IR 200 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were run on a Jeol EX-400 spectrometer (400 MHz for proton), using deuteriochloroform as a solvent and tetramethylsilane as the internal standard. Coupling constants are given in Hz. Optical rotations were determined on a Perkin Elmer Model 241 polarimeter. CD spectra were obtained on a Jasco J-700A spectropolarimeter (0.1 cm cell). GLC analyses were run on a Carlo Erba GC 8000 instrument and on a Shimadzu GC-14B instrument, the capillary columns being OV 1701 (25 m × 0.32 mm) (carrier gas He, 40 kPa, split 1:50) and a Chiraldex™ type G-TA, trifluoroacetyl γ-cyclodextrin (40 m × 0.25 mm) (carrier gas He, 180 kPa, split 1:100) or DiMePe β-cyclodextrin (25 m × 0.25 mm) (carrier gas He, 110 kPa, split 1:50). Enzymatic hydrolyses were performed using a pH-stat Controller PHM290 Radiometer Copenhagen. Mass spectra were recorded on a VG 7070 (70 eV) spectrometer. TLC's were performed on Polygram® Sil G/UV$_{254}$ silica gel precoated plastic sheets (eluant: light petroleum–ethyl acetate). Flash chromatography was run on silica gel 230–400 mesh ASTM (Kieselgel 60, Merck). Light petroleum refers to the fraction with bp 40–70 °C and ether to diethyl ether.

Dimethyl and diethyl acetylsuccinate, **9** and **10**, respectively, were purchased from Sigma-Aldrich.

4.2. Enzymatic hydrolysis

For 1 mmol of lactone in 14 mL of 0.1 M phosphate buffer, pH 7.4, the following enzymes were used: 0.150 g of porcine pancreatic lipase (PPL), 0.140 g of lipase from *Pseudomonas* species (Amano PS, 30,000 U/g), 0.052 g of lipase from *C. cylindracea* (CCL, 943 U/mg), 0.160 g of lipase from *A. niger* (Amano AP 12, 120,000 U/g), 0.400 g of lipase from *Mucor miehei* (MML, Lipozyme), 0.180 g of lipase from *C. antarctica* (Novozyme 435®, 7000 U/g), 0.230 g of porcine liver acetone powder (PLAP), 0.900 g of Horse liver acetone powder (HLAP), 0.019 g of α-chymotrypsin (α-CT, 51.8 U/mg) and 0.100 g of subtilisin (39.1 U/mg).

4.2.1. General procedure. To a solution of 0.58 mmol of the lactones **11**–**16** in 9 mL of phosphate buffer (pH 7.4) was added the enzyme, under vigorous stirring. The course of the reaction was monitored with a pH-stat, with continuous addition of 1.0 N NaOH. At ~20% conversion (addition of 0.116 mL of NaOH 1.0 N), the reaction mixture was extracted with ether to separate the unreacted lactone. The mother liquors were acidified with 5% HCl to pH 2 and extracted with ether to obtain the corresponding acids **4**–**6** or the lactone esters (**11**–**16**) derived from hydroxyacids **17**–**22**. The organic phase was dried on Na_2SO_4 and treated with diazomethane to esterify the carboxylic group before chiral HRGC analysis.

4.3. Methyl paraconate 11

Dimethyl formylsuccinate **7** (9.4 g, 0.054 mol), prepared from dimethyl succinate, sodium methoxide and methyl formate according to the literature,[21] and 0.86 g (0.023 mol) of $NaBH_4$ were stirred in 34 mL of methanol for 3 h. At the end water was added and 6 N HCl was used to neutralise the solution. The mixture was extracted with diethyl ether and the solution was dried on anhydrous Na_2SO_4. The mixture of methyl paraconate **11** and dimethyl hydroxymethylsuccinate was refluxed in benzene and a catalytic amount of PTSA to give methyl paraconate **11**, which was purified by flash chromatography. Yield 60%. IR, ^{1}H NMR, ^{13}C NMR and MS are in accordance with those reported in the literature.[27]

Methyl (+)-(*R*)-*5-oxo-tetrahydro-3-furancarboxylate* ***11***: 0.602 g of (±)-**11** was hydrolysed with 0.624 g of PPL in 50 mL of phosphate buffer according to the general procedure. After 5 h and 30 min, at ~80% conversion, the reaction was quenched and extracted with ether and the product purified by flash chromatography. Yield 18%, 92% ee (by chiral HRGC on a β-CDX column: t_R = 35.2 (*R*), t_R = 35.8 (*S*), 2 min at 100 °C, 1 °C/min → 150 °C), $[\alpha]_D^{25}$ = +40.7 (*c* 1.04, MeOH) [lit.[25] $[\alpha]_D^{25}$ = −31 (*c* 0.61, MeOH) for (*S*)-**11**], $[\alpha]_D^{25}$ = +28.9 (*c* 0.46, MeCN), $\Delta\varepsilon_{205}$ = +0.13 (CH_3CN).

4.4. Ethyl paraconate 12[8]

Ethyl paraconate **12** was synthesised following the same procedure as that used for methyl paraconate **11** using diethyl formylsuccinate **8**[8,21] prepared from diethyl succinate, sodium ethoxide and ethyl formate. The product was purified by flash chromatography (43% yield).

Ethyl (+)-(*R*)-*5-oxo-tetrahydro-3-furancarboxylate* ***12***: 0.600 g of (±)-**12** were hydrolysed with 0.570 g of PPL in 54 mL of phosphate buffer according to the general procedure. After 4 h, at about 80% conversion, the reaction was quenched and extracted with diethyl ether and the product purified by flash chromatography (16% yield). IR, cm^{-1}: 1782 (C=O), 1732 (COOEt); ^{1}H NMR, δ, ppm: 4.48 (2H, AB part of an ABX system, J_{AX} 9.2, J_{BX} 6.6, J_{AB} 9.0, H-2), 4.21 (2H, q, J 7.1, OCH_2CH_3), 3.47 (1H, m, H-3), 2.80 (2H, AB part of an ABX system, J_{AX} 8.0, J_{BX} 9.7, J_{AB} 17.9, H-4), 1.29 (3H, t, *J* 7.1, OCH_2CH_3); ^{13}C NMR, δ, ppm: 175.1 (s), 171.1 (s), 69.0 (t), 61.8 (t), 39.9 (d), 30.8 (t), 14.0 (q); MS, *m*/*z*: 158

($M^{+\cdot}$, 2), 130 (31), 129 (33), 127 (27), 115 (50), 112 (86), 100 (61), 99 (43), 98 (15), 87 (11), 85 (33), 84 (58), 83 (50), 72 (23), 68 (37), 58 (18), 56 (21), 55 (100), 44 (14), 42 (13), 41 (30), 40 (38). 93% ee (by chiral HRGC on a β-CDX column: $t_R = 39.8$ (*R*), $t_R = 40.1$ (*S*), 2 min at 100 °C, 1 °C/min → 150 °C), $[\alpha]_D^{25} = +35.8$ (*c* 1.43, MeOH), $\Delta\varepsilon_{205} = +0.23$ (CH_3CN).

4.5. Paraconic acid 4[13]

Paraconic acid (±)-**4** was obtained by hydrolysis of both methyl and ethyl paraconate (±)-**11** and (±)-**12**, under basic conditions and subsequent acidification with HCl.

(+)-(*R*)-*5-Oxo-tetrahydro-3-furancarboxylic acid* ***4***: 0.1 g of (+)-(*R*)-**12** with 93% ee was hydrolysed in 8 mL of dioxane and 4 mL of 6 N HCl at reflux for 1 h. After evaporation of the solvent water was added and the product was extracted with diethyl ether. The resulted paraconic acid (*R*)-(+)-**4** showed an ee of 80%. $[\alpha]_D^{25} = +47.1$ (*c* 0.14, MeOH) [lit.[9] $[\alpha]_D^{25} = -60$ (*c* 2.08, MeOH) for (*S*)-**4**], $\Delta\varepsilon_{207} = +0.08$ (CH_3CN).

4.6. Methyl 2-methyl-5-oxo-tetrahydro-3-furancarboxylate 13a,b

Dimethyl acetylsuccinate **9** (6.0 g, 31.9 mmol) was reduced with 0.70 g of $NaBH_4$ in 30 mL of MeOH. After 5 h water was added and the reaction mixture was extracted with diethyl ether. A mixture of the two diastereomeric lactones **13a** and **13b** was obtained in 75:25 ratio (72% yield). This ratio changed to 1:9 after equilibration with DBU in refluxing toluene for 1 h. From the two mixtures the *cis* and *trans* diastereomers were separated as pure compounds by flash chromatography.

Methyl cis-2-methyl-5-oxo-tetrahydro-3-furancarboxylate ***13a***:[28] 56% yield. IR, ^{1}H NMR and MS data are in accordance with those reported in the literature. ^{13}C NMR, δ, ppm: 174.8 (s), 170.6 (s), 76.2 (d, C-2), 52.2 (q), 44.4 (d, C-3), 31.2 (t, C-4), 16.8 (q). HRGC (γ-CDX) (150 °C isothermal): $t_R = 19.8$ min (2*R*,3*R*), 22.6 (2*S*,3*S*).

Methyl trans-2-methyl-5-oxo-tetrahydro-3-furancarboxylate ***13b***:[28] 58% yield. IR, ^{1}H NMR and MS data are in accordance with those reported in the literature. ^{13}C NMR, δ, ppm: 174.1 (s), 171.0 (s), 78.0 (d, C-2), 52.5 (q), 47.1 (d, C-3), 32.1 (t, C-4), 20.5 (q). HRGC (γ-CDX) (150 °C isothermal): $t_R = 13.6$ min (2*S*,3*R*), 15.0 (2*R*,3*S*).

4.7. Ethyl 2-methyl-5-oxo-tetrahydro-3-furancarboxylate 14a,b

Diethyl acetylsuccinate **10** (6 g, 27.7 mmol) was reduced with 0.68 g of $NaBH_4$ in 26 mL of EtOH. After 5 h water was added and the reaction mixture was extracted with diethyl ether. A 3:2 mixture of the two lactones **14a** and **14b** was obtained (80% yield after chromatographic separation). After equilibration of the mixture with DBU under refluxing toluene for 1 h the ratio was 90:10 in favour of the *trans* isomer **14b**.

Ethyl cis-2-methyl-5-oxo-tetrahydro-3-furancarboxylate ***14a***:[29] 52% yield. IR and ^{1}H NMR data were in accordance with those reported in the literature.[29b] ^{13}C NMR, δ, ppm: 174.9 (s), 170.1 (s), 76.3 (d, C-2), 61.4 (t), 44.5 (d, C-3), 31.1 (t, C-4), 16.7 (q), 14.1 (q); MS, *m*/*z*: 172 ($M^{+\cdot}$, 2), 128 (11), 127 (30), 126 (18), 113 (11), 100 (47), 99 (18), 83 (13), 55 (100), 43 (28). HRGC (γ-CDX) (150 °C isothermal): $t_R = 21.9$ min (2*S*,3*R*), 25.1 (2*R*,3*S*).

Ethyl trans-2-methyl-5-oxo-tetrahydro-3-furancarboxylate ***14b***:[29] 54% yield. IR and ^{1}H NMR data were in accordance with those reported in the literature.[29b] ^{13}C NMR, δ, ppm: 174.3 (s), 170.5 (s), 78.1 (d, C-2), 61.6 (t), 47.3 (d, C-3), 32.1 (t, C-4), 20.6 (q), 13.9 (q); MS, *m*/*z*: 172 ($M^{+\cdot}$, 2), 157 (4), 144 (9), 130 (28), 127 (19), 101 (40), 100 (34), 83 (10), 73 (15), 55 (100), 43 (34). HRGC (γ-CDX) (150 °C isothermal): $t_R = 14.9$ min (2*R*,3*R*), 15.7 (2*S*,3*S*).

4.8. 2-Methyl-5-oxo-tetrahydro-3-furancarboxylic acid 5a,b

Lactones (±)-**13a** and (±)-**13b** were hydrolysed separately under acidic conditions (6 N HCl, dioxane, reflux) to give the corresponding lactonic acids (±)-**5a** and (±)-**5b** in quantitative yield.

cis-2-Methyl-5-oxo-tetrahydro-3-furancarboxylic acid ***5a***: solid, mp 104–106 °C; IR, cm^{-1}: 3200 (OH), 1754, 1733; ^{1}H NMR, δ, ppm: 5.08 (1H, br s, OH), 4.89 (1H, quintet, *J* 6.8, H-2), 3.50 (1H, q, *J* 7.4, H-3), 2.95 (1H, dd, J_1 6.2, J_2, 17.6, H-4), 2.70 (1H, dd, J_1 8.6, J_2 17.6, H-4), 1.43 (3H, d, *J* 6.6, CH_3); ^{13}C NMR, δ, ppm: 175.0 (s), 174.6 (s), 76.1 (d, C-2), 44.4 (d, C-3), 31.4 (t, C-4), 16.8 (q); MS, *m*/*z*: 129 ($M-CH_3$, 11), 101 (17), 100 (42), 99 (12), 85 (12), 83 (18), 82 (12), 73 (15), 72 (19), 63 (12), 57 (17), 56 (16), 55 (100), 54 (11).

trans-2-Methyl-5-oxo-tetrahydro-3-furancarboxylic acid ***5b***: solid, mp 86 °C; IR, cm^{-1}: 3200 (OH), 1754, 1733; ^{1}H NMR, δ, ppm: 9.1 (1H, br s, OH), 4.74 (1H, quintet, *J* 6.5, H-2), 3.08 (1H, m, H-3), 2.96 (1H, AB part of an ABX system, J_1 9.0, J_2, 17.6, H-4), 2.86 (1H, AB part of an ABX system, J_1 9.5, J_2 17.6, H-4), 1.55 (3H, d, *J* 6.2, CH_3); ^{13}C NMR, δ, ppm: 175.8 (s), 174.5 (s), 78.1 (d, C-2), 47.1 (d, C-3), 32.0 (t, C-4), 20.7 (q); MS, *m*/*z*: 144 ($M^{+\cdot}$, 1), 129 (11), 116 (14), 103 (50), 101 (57), 99 (27), 85 (23), 73 (30), 72 (32), 56 (25), 55 (100), 43 (32), 29 (11).

4.9. Reduction of 8 with baker's yeast

To 2 mmol of the ketodiester **8**, 20 g of raw baker's yeast in 40 mL of tap water (preincubated at 50 °C for 30 min) were added under stirring. The reaction mixture was monitored by HRGC. When the reaction did not proceed any further, the mixture was continuously extracted

with diethyl ether for 48 h and dried over anhydrous Na_2SO_4. The corresponding hydroxy diester **23** was obtained as pure compound. ^{1}H NMR, δ, ppm: 4.20, 4.15 (4H, 2q, $2OCH_2CH_3$), 3.80 (2H, apparent d, CH_2OH), 3.6 (1H, vbr s, OH), 3.30 (1H, quintet, J 6.0, $CHCH_2OH$), 2.75, 2.63 (2H, AB part of an ABX system, J_1 17.5, $J_2 = J_3$ 6.0, $CHCH_2CO_2Et$), 1.27, 1.26 (6H, 2t, CH_3); ^{13}C NMR, δ, ppm: 173.4 (s), 171.9 (s), 62.6 (t), 61.0 (t), 60.8 (t), 43.6 (d), 32.9 (t), 14.08 (q), 14.06 (q). Lactonisation of **23** into **12** was accomplished on heating in toluene.

4.10. Reduction of 10 with baker's yeast

To 2 mmol of the ketodiester **10**, 20 g of raw baker's yeast in 40 mL of tap water (preincubated at 50 °C for 30 min) were added under stirring. The reaction mixture was monitored by HRGC. When the reaction did not proceed any further, the mixture was continuously extracted with diethyl ether for 48 h and dried over anhydrous Na_2SO_4. A 1:1 mixture of the diastereomeric *syn* and *anti* hydroxy diesters **26** and **27** was isolated. ^{1}H NMR, δ, ppm: 4.60, 4.11, 4.10 (4H, 3q, $2OCH_2CH_3$), 4.07, 4.02 (1H, m, $2CHOH$), 3.3 (1H, vbr s, OH), 2.88 (1H, m, $CHCHOH$), 2.72, 2.62 (1H, AB part of an ABX system, J_1 16.0, $J_2 = J_3$ 6.0, $CHCH_2CO_2Et$), 2.70, 2.59 (1H, AB part of an ABX system, J_1 16.0, $J_2 = J_3$ 5.0, $CHCH_2CO_2Et$), 1.24, 1.22 (6H, 2t, CH_3), 1.19, 1.18 (3H, 2d, CH_3); ^{13}C NMR, δ, ppm: 173.4 (s), 173.3 (s), 172.3 (s), 171.9 (s), 67.7 (d), 67.5 (d), 60.9 (t), 60.7 (t), 48.2 (d), 48.0 (d), 32.8 (t), 31.7 (t), 20.6 (q), 20.5 (q), 14.1 (q), 14.0 (q). This mixture was refluxed in toluene to give a 1:1 mixture of the two lactones (−)-**14a** and (−)-**14b**, which were separated on column chromatography.

Ethyl (2S,3S)-(−)-2-methyl-5-oxo-tetrahydro-3-furancarboxylate ***14a***: 24% yield; $[\alpha]_D^{25} = -89.1$ (c 0.54, CH_3CN), $\Delta\varepsilon_{223} = +0.21$ (CH_3CN), >99% ee.

Ethyl (2S,3R)-(−)-2-methyl-5-oxo-tetrahydro-3-furancarboxylate ***14b***: 22% yield; $[\alpha]_D^{25} = -30.0$ (c 0.64, CH_3CN), $\Delta\varepsilon_{222} = -0.33$ (CH_3CN), >99% ee.

The optically active lactone (−)-**14a** (0.107 g) was refluxed in 8 mL of dioxane and 4 mL of 6 N HCl for 1 h. After evaporation of the solvent diethyl ether was added and the crude reaction mixture was washed with saturated $NaHCO_3$. The mother liquors were then acidified with HCl and extracted with diethyl ether to give the optically active acid (−)-**5a** (47% yield) (>99% ee).

(2S,3S)-(−)-2-Methyl-5-oxo-tetrahydro-3-furancarboxylic acid ***5a***: mp 124–125 °C; $[\alpha]_D^{25} = -92.0$ (c 0.68, CH_3CN), $\Delta\varepsilon_{227} = +0.13$ (CH_3CN).

The optically active lactone **14b** (0.107 g) was refluxed in 8 mL of dioxane and 4 mL of 6 N HCl for 1 h. After evaporation of the solvent diethyl ether was added and the crude reaction mixture was washed with saturated $NaHCO_3$. The mother liquors were acidified with HCl and extracted with diethyl ether to give the enantiomerically pure acid (−)-**5b** (67% yield) (>99% ee).

(2S,3R)-(−)-2-Methyl-5-oxo-tetrahydro-3-furancarboxylic acid ***5b***: mp 120–121 °C; $[\alpha]_D^{25} = -34.3$ (c 0.70, CH_3CN), $\Delta\varepsilon_{226} = -0.26$ (CH_3CN).

Esterification of (−)-**5a** and (−)-**5b** with MeOH and trimethylchlorosilane[30] gave the corresponding methyl esters (−)-**13a** and (−)-**13b**, which were also isolated from the bioreduction of dimethyl acetylsuccinate **9** under the same conditions used for the diethyl derivative **10**.

Methyl (2S,3S)-(−)-2-methyl-5-oxo-tetrahydro-3-furancarboxylate ***13a***: (>99% ee), $[\alpha]_D^{25} = -77.1$ (c 0.14, CH_3CN), $\Delta\varepsilon_{223} = +0.16$ (CH_3CN).

Methyl (2S,3R)-(−)-2-methyl-5-oxo-tetrahydro-3-furancarboxylate ***13b***: (>99% ee), $[\alpha]_D^{25} = -34.4$ (c 0.16, CH_3CN), $\Delta\varepsilon_{222} = -0.30$ (CH_3CN).

4.11. Methyl and ethyl terebate 15 and 16

Methyl terebate **15** and ethyl terebate **16** were synthesised according to the literature.[17] A mixture of 11 g (0.17 mol) of zinc powder (previously activated) and 17 g (0.10 mol) of isopropyl iodide in 90 mL of acetonitrile was refluxed under stirring for 0.5 h under an atmosphere of argon. A solution of 4.6 mL (0.037 mol) of dimethyl maleate (diethyl maleate), 5.4 mL (0.074 mol) of anhydrous acetone and 20 mL of anhydrous acetonitrile were then added and after refluxing for further 3 h, the reaction mixture was let to reach the room temperature and the zinc was filtered. The organic layer was poured into 30 mL of saturated aqueous solution of NH_4Cl and extracted with diethyl ether. The combined ethereal solution was dried over anhydrous Na_2SO_4. The crude reaction mixture was purified by flash chromatography on silica gel and a mixture of ethyl acetate and light petroleum (5% up to 20% in ethyl acetate) as eluant (89% yield).

Methyl 2,2-dimethyl-5-oxo-tetrahydro-3-furancarboxylate ***15***: IR, ^{1}H NMR and MS spectra were identical with those reported in the literature.[28] ^{13}C NMR, δ, ppm: 173.9 (s), 170.2 (s), 84.3 (s, C-2), 52.3 (q), 50.2 (d, C-3), 31.7 (t, C-4), 28.3 (q), 23.2 (q).

Ethyl 2,2-dimethyl-5-oxo-tetrahydro-3-furancarboxylate ***16***: oil, IR, cm^{-1}: 1781, 1735; ^{1}H NMR, δ, ppm: 4.22 (2H, q, OCH_2CH_3), 3.15 and 2.70 (2H, AB part of an ABX system, J_{AB} 17.6, J_{AX} 9.9, J_{BX} 8.4 H-4), 1.61 (3H, s, CH_3), 1.33 (3H, s, CH_3), 1.31 (3H, t, OCH_2CH_3); ^{13}C NMR, δ, ppm: 174.0 (s), 169.7 (s), 84.3 (s, C-2), 61.5 (t), 50.4 (d, C-3), 31.7 (t, C-4), 28.4 (q), 23.2 (q), 14.1 (q); MS, m/z: 170 (32), 142 (30), 140 (12), 128 (21), 127 (22), 112 (16), 100 (44), 99 (29), 68 (35), 55 (100), 43 (79).

Methyl (S)-(−)-2,2-dimethyl-5-oxo-tetrahydro-3-furancarboxylate ***15***: 1.23 g (7.15 mmol) of methyl terebate (±)-**15** was hydrolysed with HLAP (4.9 g) in 100 mL of phosphate buffer at pH 7.4. After 60% conversion, the mixture was extracted with diethyl ether. The resulting methyl terebate, having 48% ee was hydrolysed again

with HLAP to a conversion of 35%. The same work up was followed and methyl terebate with 76% ee was obtained. $[\alpha]_D^{25} = -3.2$ (c 1.70, CH_3CN), $\Delta\varepsilon_{218} = +0.82$ (CH_3CN).

(*S*)-(−)-*2,2-Dimethyl-5-oxo-tetrahydro-3-furancarboxylic acid* ***6***: 0.181 g of methyl terebate (−)-**15** with 76% ee was hydrolysed in 13 mL of dioxane and 7 mL of 6 N HCl under reflux for 1 h. After evaporation of the solvent, a solution of aqueous $NaHCO_3$ was added and extracted with ether. The mother liquors were acidified with 6 N HCl and extracted with diethyl ether. The organic phase was dried over Na_2SO_4. The terebic acid obtained was recrystallised from ethyl acetate (60% yield), 60% ee. Mp 177–179 °C (lit.[24] 198 °C); $[\alpha]_D^{25} = -7.3$ (c 0.49, acetone) [lit.[24] $[\alpha]_D^{25} = -13.7$ (c 1.05, acetone)], $\Delta\varepsilon_{220} = +0.57$ (CH_3CN).

Ethyl (*S*)-(−)-*2,2-dimethyl-5-oxo-tetrahydro-3-furancarboxylate* ***16***: (±)-**16** was hydrolysed with HLAP to high conversion values following the general procedure. Extraction with diethyl ether under basic conditions gave (−)-**16** with 63% ee, $[\alpha]_D^{25} = -4.3$ (c 1.09, CH_3CN), $\Delta\varepsilon_{218} = +0.59$ (CH_3CN).

Acknowledgements

Financial supports by the M.I.U.R., PRIN 2002 and the University of Trieste are gratefully acknowledged.

References and notes

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